Response to FDA Draft Guidance Statement on Research into the Treatment of Life-threatening Emergency Conditions using Exception to Informed Consent

The NIH/NHLBI Resuscitation Outcomes Consortium (ROC) Investigators' Perspective

Sudden, unexpected out-of-hospital cardiac arrest and major trauma claim hundreds of thousands of lives per year and share many common physiological mechanisms and challenges. From a public health standpoint, cardiac arrest and major trauma have no equals. The numbers of people dying from these conditions are staggering --- equivalent to one or two jumbo jets full of passengers crashing and killing everyone on board every day of the year. Cardiac arrest and major trauma can strike virtually anyone, from cradle to grave, with no warning and within an instant turn a healthy, productive person into a victim only minutes from biological death. Despite what the American media depict on TV where almost 70% of cardiac arrest victims receiving CPR make it out of the hospital alive and well (1), the actual odds of surviving a sudden, unexpected, out-of-hospital cardiac arrest in the United States are only about 5% --- 1 in 20, not 3 out of 4. In large cities, like New York and Chicago, where traffic congestion and high rise buildings make it difficult for emergency crews to reach victims quickly, reported survival from cardiac arrest averages only 1 in 100. (2) (3) Major trauma victims are not much better off. Approximately 175,000 injury-related deaths occur in North America each year and life-threatening traumatic injury is the leading cause of death for persons 1-44 years of age.

We represent the National Institutes of Health/National Heart Lung, Blood Institute (NIH/NHLBI) sponsored Resuscitation Outcomes Consortium (ROC), which is a nearly two-year old, $50 million governmentally sponsored, clinical trials network with a mission of conducting adequately powered, randomized clinical trials that can determine whether promising drugs, devices, and therapeutic strategies can improve neurologically intact survival from out-of-hospital cardiac arrest and major traumatic injury. The Consortium includes investigators, study coordinators, and public safety/emergency care providers from 11 (8 U.S., 3 Canadian) different geographic areas. Like our colleagues in the

Neurological Emergencies Treatment Trials (NETT) and Pediatric Emergency Care Applied Research Network (PECARN), our clinical investigators and their teams have extensive experience with the exception to informed consent procedures, not just in recently launched and developing ROC trials, but from roles that many of them played as investigators, clinical trial leaders, emergency care directors or public safety personnel in prior studies such as the Public Access Defibrillation (PAD) trial(4), the ASPIRE study(5), and the recently completed Polyheme study. We appreciate the opportunity to provide our input on the FDA's draft guidance relating to the Exception from Informed Consent Requirements for Emergency Research.

In general, the ROC investigators believe the existing exception to informed consent procedures for emergency research strike an appropriate balance between the need to find more effective, safe treatments for imminently life-threatening, incapacitating conditions and the rights of individuals in our society. Our experience is that the criteria for allowing studies under § 50.24 provides adequate protection of human subjects and permits conduct of scientifically rigorous research. The existing regulations and the draft guidance document are generally well written and of great value to investigators seeking to conduct such research with the highest moral and ethical standards, particularly in the areas of study design and execution, public disclosure, and community consultation.

1. The ROC investigators support the opinions and recommendations expressed by our colleagues in NETT and will not repeat or elaborate further on their points today. We believe that a Central IRB or other experienced national panel could be considered as an option for advising local IRBs that either have little experience with the emergency exception process and/or are struggling with a particularly challenging issue. However, we do not support requiring all proposals to be reviewed by a Central IRB because we are concerned that it may delay implementation of important research studies without adding significant value to the process.

Since the majority of ROC study populations are adult, we will target our comments primarily to research on adults, knowing that many of the important, unique issues pertaining to emergency research in children are being addressed by the PECARN investigators' comments. We will focus our comments on two issues and provide brief answers to the questions posed in the consent notice in the Appendix to this document:

1. The need to stratify the intensity of community consultation and public disclosure based upon the anticipated incremental risks to subjects of participating in a research study.

A major purpose of the FDA draft document is to provide guidance to investigators, IRBs, sponsors, and others on implementation of community consultation and public disclosure. A number of the questions being asked of this meeting's participants center on whether there should be a minimum level of community consultation (question #7), or required public disclosure elements pre- (question #12) or post- (question #14) study. We support the position of our colleagues from the American Heart Association and agree that there should be minimum guidelines for each of these areas, but that the minimum levels of community consultation and public disclosure should be based on the incremental risk associated with the study interventions. For example, a trial of an intervention already FDA-approved for the indication being studied should require less extensive community consultation and public disclosure actions than studies of unapproved interventions, particularly if the latter involve a drug, device, and/or therapeutic strategy with clinically significant inherent risk as judged by the IRB. For a high incremental risk study, more community consultation should be required, including an appropriate number of mass media solicitations, community meetings, and contact with prominent community organizations. Random digit dialing phone surveys could be

considered to sample whether the messages are reaching the community effectively in high incremental risk studies. Individual IRBs should set their own standards based on their perception of the community needs and sensitivities. Involvement of the community should include attempts to consult with targeted, at-risk, or interested, populations.

2. Exception from consent for emergency research should extend to review of the medical record to the time of hospital discharge as the standard in emergency research.

21 CFR 50.24(b) currently states that "IRBs must ensure there are procedures in place to provide information about the emergency research study, at the earliest feasible opportunity, to (1) the subject, if the subject's condition permits this, (2) the subject's legally authorized representative (if the subject remains incapacitated), or (3) the subject's family member (if no legally authorized representative is available), including notice that participation in the study may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled (21 CFR 50.24(b))."

The ROC investigators agree with these requirements, but suggest an important modification that would permit the exception from consent for emergency research to extend to review of the medical record to the time of hospital discharge as the standard in emergency research. Once the experimental intervention has occurred, the physical risk of inflicting harm (whether evident immediately or after some delay) from study participation is over. Currently, when a patient or other suitable representative as defined in 21 CFR 50.24(b) is informed that the patient was a subject in a research study under the emergency exception to informed consent, they are given the option to

withdraw or discontinue participation in the study. We agree that standard, written informed consent procedures must be followed for further interactions with the patient or their family (i.e., follow-up interviews, tests, or other evaluations). However, as discussed in a recent paper by several of our ROC leaders and team members(6), review of the clinical record is necessary to determine important outcomes such as survival to discharge. If consent is required for this review but not granted, then these data are missing during analysis. Since seriously ill or disadvantaged patients may be less likely to assent, then investigators cannot determine reliably whether these vulnerable patients were harmed by the intervention. If missing data are different from complete data, then the analysis is susceptible to bias, and the conclusions could be misleading. Thus without access to subject records for review, the investigators will be unable to ensure timely safety review, and study results are likely to be biased significantly.

This is not just a theoretical concern, but is a common problem in clinical trials that involve patients at high risk of death or other adverse events. The NIH-sponsored Public Access Defibrillation trial required investigators to train >19,000 volunteer lay rescuers from 993 community units in 24 North American regions. (4) There were more survivors to hospital discharge in the units assigned to have volunteers trained in CPR plus the use of AEDs (30 survivors among 128 arrests) than there were in the units assigned to have volunteers trained only in CPR (15 among 107; P=0.03; relative risk, 2.0; 95 percent confidence interval, 1.07 to 3.77). Had only a couple of patients or families denied consent for the investigators to determine whether the patient survived to hospital discharge, this landmark positive trial would have appeared negative, since it is

customary for an experimentally treated patient whose outcome is unknown to be assigned the worst outcome (i.e., death) and control patients the best outcome (i.e., survival).

Another example is the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial, which sought to determine the efficacy of dual-chamber pacing compared with backup ventricular pacing in patients with standard indications for ICD implantation but without indications for antibradycardia pacing. (7) Extrapolation from non-consent rates in resuscitation studies to results from the DAVID trial demonstrates that missing data due to lack of assent could influence whether there is a significant difference between treatment groups (survival of control vs. intervention: p=0.04 for complete data; p=0.08 for 10.8% lack of assent; p=0.40 for 19.7% lack of assent).

We believe that the solution to this dilemma is to extend the exception from consent for emergency research rule to include review of the clinical record upon hospital discharge as the standard in emergency research. The only potential risk to patients associated with review of the clinical record after the intervention is loss of privacy and confidentiality. We believe that appropriate safeguards already exist under HIPAA to minimize this risk.

Finally, our ROC leaders and investigators cannot emphasize enough how critical it is for clinical research to continue to make progress in treating life-threatening emergency conditions such as cardiac arrest, trauma, and other acute, incapacitating disorders. The public health consequences of these medical and surgical emergencies are staggering, and we as a society have a moral and ethical obligation to find more effective and safe therapies. It is not possible to conduct life-saving research in the

prehospital emergency setting without the provision for exception to informed consent. We applaud and appreciate the efforts of DHHS and the FDA in soliciting input on the Draft Guidance relating to the Exception from Informed Consent Requirements for Emergency Research. We believe that, with relatively minor modification, the Regulations and Draft Guidance strike a reasonable balance between the need to conduct ethical, potentially life-saving research to find more effective treatments for critically ill and/or injured subjects and the need for human subject protections.

References

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4. Hallstrom AP, Ornato JP, Weisfeldt M, Travers A, Christenson J, McBurnie MA, et al. Public-access defibrillation and survival after out-of-hospital cardiac arrest. N Engl J Med 2004;351(7):637-46.

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Appendix

The ROC leaders and investigators brief responses to the questions posed in the consent notice.

2. Are the criteria for allowing studies conducted under §50.24 adequate to protect human subjects and to promote scientifically rigorous research? ***Yes. The criteria are rigorous but necessary and can be followed by competent clinical trial investigators.*** Are any additional criteria warranted? ***No.***
3. Are the following criteria easily understood and, if not, how can they be clarified?

    a. "Available treatments are unsatisfactory or unproven" (§ 50.24(a)(1))

    b. "Prospect of direct benefit" (§50.24(a)(3))

    c. "Practicably" (§50.24(a)(4))

    We believe they are clear as written with the exceptions noted in the comments by our NETT study colleagues.

4. Are there other criteria in the regulation, besides those identified in criteria (2)(a) through (c), that need to be clarified? ***No.***
5. Are there challenges that have not been explicitly addressed in the regulation in designing scientifically rigorous and ethically sound emergency research protocols (e.g., pediatric protocols)? If there are such challenges, should they be addressed and how? ***We believe there are huge challenges in the area of pediatric emergency research using the exception to informed consent, but defer to our colleagues PECARN investigators.***
6. What are the costs, benefits, and feasibility of community consultation as currently required under § 50.24? ***In our experience, the costs of***

community consultation are generally modest in relation to its benefits and importance. As stated above, we believe that the amount of community consultation required should be at the discretion of the IRB, and should vary based on the degree of incremental risk involved in the study as well as the unique risks and sensitivities of the community. In the Public Access Defibrillation trial (8), the primary IRBs for all 24 trial sites and a total of 101 IRBs approved the study. The median interval from submission to approval was 108 days (IQR 43-196), and the mean number of revisions was two (range 0-7). Investigators conducted nearly 12,000 activities to achieve community consultation and public disclosure, although activities varied greatly from site to site in both type and quantity.

7. What aspects of community consultation as currently practiced are effective mechanisms for human subject protection? Are there additional practices that could enhance human subject protection? ***We believe the most valuable form of community consultation comes from individuals and groups who are either demographically similar to the study subjects and/or who have similar risk factors or actual medical conditions as the expected study subjects. For example, some of the most valuable community input, advice, and ultimately support in the PAD trial came from members of "Mended Hearts" groups, which are composed of individuals with known heart disease who have survived heart attacks, cardiac arrest, or various cardiac surgical procedures. We believe that input from such medically relevant populations is much more meaningful than from individuals or groups who have a particular opinion (positive or negative) on whether research should be generally permitted using the exception to informed consent based upon personal preferences.***
8. Are there elements of community consultation, both procedural and substantive, that should, at a minimum, be required (e.g., types of information

presented, number and types of meetings or interactions, number of people reached)? ***Please see the body of our main presentation above.***

9. Would opt-out mechanisms (e.g., advanced directives, jewelry similar to medical alert bracelet/necklace, and driver's license indicators) to identify individuals who do not wish to be included as subjects in particular emergency research studies provide a necessary protection for human subjects? If so, are they feasible? ***Medic alert type bracelets and/or necklaces have some limited value and should be offered as an opt-out mechanism for those who do not wish to participate in emergency research studies with the exception to informed consent. It cannot be guaranteed that firefighters, EMTs, and paramedics will always notice such identifiers, even though every effort should be made to train them to do so. It is highly unlikely that they will find an "opt-out" identifier in a purse or wallet, since their first priority will be to provide medical care to the patient and it is often against EMS agency policy to look through the patient's personal belongings during a resuscitation.***
10. Who should use the information obtained from the community consultation process and how should they use it? Should the regulation be more specific on this point, and if so, what should it provide? ***We believe the regulations are adequate on this question: the IRB should consider the information as important input on their decision as to whether a proposed study should be approved, modified, or rejected.***
11. Are there others besides the IRB (e.g., sponsors, clinical investigators, community leaders, advisory committees, ethicists) who should play a role in determining the adequacy of the plan for community consultation and the material to be publicly disclosed? ***We believe that a Central IRB or other experienced national panel could be considered as an option for advising local IRBs that either have little experience with the emergency exception process and/or are struggling with a particularly challenging issue. However, we do not support requiring all proposals to be reviewed by a Central IRB because we are concerned that it may delay implementation of important research***

studies without adding significant value to the process.

12. The community consultation process typically includes meetings and discussions about the study with the community. Should the regulation require documentation of meeting activities and discussions in sufficient detail to show the information that was disclosed and the community reaction to the clinical investigation? If so, who should be responsible for such documentation (e.g., clinical investigator, sponsor)? ***Each IRB must determine how it will review and use the information from community consultation activities. Options for information collection include 1) attendance of such meetings by local IRB representatives; 2) review of a log of individuals attending the meetings; 3) reviewing a record (either on audio or videotape) of the proceedings; 4) reviewing a written summary of the proceedings for the IRB; and 5) reviewing a written transcript of the proceedings, if requested in advance by the IRB. Such information should be summarized by the IRB in its proceedings,***
13. The regulations (see 21 CFR 312.54(a) and 812.47(a)) currently require the sponsor to submit the information publicly disclosed prior to study initiation and after completion to FDA Docket Number 1995S0158 (formerly 95S-0158). Should the regulation also require that documentation of community consultation activities be submitted to FDA, for example by being placed in the public docket? If so, who should be responsible for doing this? ***We believe this is not necessary and should remain a responsibility of the IRB.***

    Should this information also be available elsewhere such as on *clinicaltrials.gov*?[2] ***No.***
14. Are there certain types of information (e.g., adverse event reports, study protocol, informed consent document) that should, at a minimum, be publicly disclosed to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn? ***No. This task***

should remain the responsibility of the local IRB.

15. Should the full protocol, or other information such as the investigator's brochure, for emergency research be available (e.g., through FDA's public docket, *clinicaltrials.gov)* to the general public before initiation of the clinical investigation? ***No. Issues of proprietary concern will be difficult to address were this to happen and could be perceived as a significant barrier to research.***
16. Is there information regarding study results that, at a minimum, should always be disclosed after the clinical investigation is completed? If so, what is that information? ***The main results and conclusions of the study, any significant adverse effects that were found, and implications for future treatment of victims with a similar problem. This information is currently shared with the local IRB and could be shared locally if believed warranted by the local IRB. Mandating such disclosure will add an unnecessary burden to this currently effective process.***
17. How can this disclosure best be accomplished? Who should be responsible for this disclosure? ***The investigators currently have the responsibility to provide the disclosure. After publication of the main results, this is best accomplished by a press release followed by news reports and interviews of the investigators.***
18. When should a clinical investigation be considered "completed?" How soon after a clinical investigation is completed should the results be disclosed? ***The investigation should be considered “completed” after all primary data are collected, analyzed, and published in a peer-reviewed journal. The results should be disclosed to the scientific community by publication in an appropriate peer-reviewed journal at the earliest feasible date.***
19. How can we assure timely disclosure of study results after completion of a study? ***You can’t, other than relying on the normal scientific disclosure and peer review process. Premature release of study findings will only***

result in confusion and the risk of actions being based upon incomplete or potentially incorrect information.

20. What type of venue would be best for this additional review and public discussion? ***N/A. This already happens following publication of study results.***
21. What information should be included in this review? ***N/A.***
22. Are there any additional challenges to the conduct of emergency research that have not been identified in the preceding questions? If so, what are they and how should they be addressed? ***Please see responses in main body of text above.***